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EXAMINER	
NOBLE, MARCIA STEPHENS	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/561,780	KOLOSSOV ET AL.	
	Examiner	Art Unit	
	MARCIA S. NOBLE	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 November 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,11,15,16,26,40-42,45,49 and 70-75* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,11,15,16,26,40-42,45,49 and 70-75* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 November 2009* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Withdrawn Rejections/Objections

The objection to the disclosure because of the following informalities: The specification comprises typographical errors on p. 16, line 25, which recites "that the those are get rid of..." and line 27, which recites "enbryonic", is withdrawn. Applicant amended the disclosure to correct these recitations.

The objection to the drawings as failing to comply with 37 CFR 1.84(p)(5) because the brief description of the figures in the specification Figure 2A and 2B, and the drawings disclosure Figure 2 and Figure 2 continued and does not disclose A and B, is withdrawn. Applicant filed replacement drawings to correct the discrepancy between the drawing and the specification.

The objection to claims 1-9, 15, 16, 4-42, 45, 49, and 70-75 are objected to because of these claims comprise non-elected subject matter, is withdrawn. Applicant amended the claims to only encompass elected subject matter.

The rejection of claims 40-42, rejected under 35 U.S.C. 112, second paragraph, as being indefinite for the recitation, "the...cell aggregates", which lacks sufficient antecedent basis, is withdrawn. Applicant amended the claims to remove this recitation.

The rejection of claim 73, rejected under 35 U.S.C. 112, second paragraph, as being indefinite for the recitation, "the container", which lacks sufficient antecedent basis, is withdrawn. Applicant amended the claim 73 to depend from claim 72, which recites "a container".

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-5, 40-42, and 49, as amended or previously presented, are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 3-7 of copending Application No. 11/547,871. Although the conflicting claims are not identical, they are not patentably distinct from each other because the methods of the instant claims are disclosed by the methods of the copending claims.

Copending claim 3 discloses an assay system that cultivates a biological material derived from tissue or tissue-like structures obtained by culturing an ES cell derived first cell type in the presence of at least one embryonic second cell type. Claim 1 of the instant claims is drawn to the method of making the above described biological material.

Thus, it would be obvious to an artisan that the method step disclosed in claim 3 of the copending application is the same method as claim 1 of the instant application. Dependent claims 4-7 of the copending application are essentially identical to dependent claims 2-5 of the instant application. Claim 40 of the instant application further comprises analyzing physiological status of the tissue or tissue-like structure. Claim 41 and 42 of the instant application specify that the analyzing step encompasses measuring electrical activity with a microelectrode array. Copending claim 3 discloses measuring electrical activity with an electrode array. Thus, Copending claim 3 discloses the same scope of claims 40-42 of the instant application. Claim 49 of the instant application discloses the use of tissue system of claim 1 for analyzing the influence of factors and compounds. These limitations are disclosed as an intended used in the preamble of claim 3 of the copending application. Thus, it would be obvious to an artisan of ordinary skill that the instant and copending claims of the two applications encompass the same invention.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1, 6, 8, 11, 15, 16, 26, 45, and 49, as amended or previously presented, are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 3, 17, 21-24, 26-32, 47, 55, 57-62, 64-69, and 70 of copending Application No. 10/594,188. Although the conflicting claims are

not identical, they are not patentably distinct from each other because the claims encompass overlapping, non-mutually exclusive scopes.

Copending claims 3 and 47 are drawn to method that cultures ES cells to form EB. Claim 1 of the instant application is drawn to a method that cultures a first embryonic-derived cell type with a second embryonic cell type and aligning or integrated the cell types to form a tissue-like structure. The breadth of claim 1 encompasses culturing a plurality of ES cells together because the claim does not specify that the first and second cell types are two different cell types. Claim 1 does not specify the characteristics of a "tissue-like structure". Thus, producing an EB, as claimed in copending claims 3 and 47, encompasses the limitations of aligning and integrating cells into a "tissue-like structure" of instant claims 1. Thus, Copending claims 3 and 47 encompass the same limitations as encompassed by instant claim 1. Copending claims 17 and 55 encompass the same limitations as instant claims 9 and 10 because both the copending and instant claims specify that the method produce cardiomyocytes in the EB or tissue-like structure. Copending claims 21, 22, 24, 57, 58, and 60 encompass the same scope as instant claims 2 and 4 of the instant applications because both recites that the ES cell have a selectable marker and a reporter gene both operably linked to a tissue specific marker. Copending claims 23 and 59 have the same scope as instant claim 3 because specify the selectable marker as puromycin. Copending claims 26 and 62 and instant claim 6 specify the reporter gene is EGFP. Copending claims 27 and 61 and instant claim 5 encompass the same scope because all claims specify the tissue specific promoter is substantially the same for the selectable marker and the reporter

gene. Copending claims 28 and 64 and instant claim 8 encompass the same scope because both claims specify that the marker and reporter gene are contained in the same cistron. Copending claims 29, 30, 65, 66, 69, and 70 of the copending application encompass the same scope as instant claims 11 and 26 because all the claims specify the promoter as a cardiac specific promoter, more specifically alpha-MHC or MLC2v. Copending claims 31, 32, 67, and 68 encompass an EB, cardiomyocytes, or tissue of cardiomyocytes. These limitations are a species of the co-culture of instant claim 15, the tissue of instant claim 16, and the tissue of instant claim 45. Instant claims 49 specifies intended use of the method of claim 1 and does not add any active steps to the method. Thus, copending claims 3 and 47 encompass the same scope as claim 49 for reasons discussed above. Overall, it would be obvious to an artisan that the claims of the instant and copending application encompass the same invention because they encompass overlapping, non-mutually exclusive scopes.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Arguments

In Applicant's response, Applicant request that the double patenting rejections be held in abeyance until subject matter that is otherwise allowable is identified. At this time Applicant will filed a terminal disclaimer.

Applicant's request is granted and the double patenting rejections of record are maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 4, 5, 7, 8, 11, 15, 16, 26, 40, 41, 45, 49, and 70-73, as amended or previously presented, are rejected under 35 U.S.C. 102(b) as being anticipated by Muller (Muller et al. FASEB J 14:2540-2548; of record), as evidenced by Itskovitz-Eldor (Itskovitz-Eldor et al. Molecular Medicine 6(2):88-95, 2000).

Given its broadest reasonable interpretation, claim 1 and dependents encompass a method of making an EB. Amended claim 1 species the coculture cardiomyocytes derived from ES cells, fibroblast cells, and endothelial cells. The claims do not require that the three cell types come from different sources or that only these three cell types be present. EB ultimately spontaneously differentiate into a mixture of all cell types (Itsckovitz-Eldor, p. 89, col 1, lines 9-23), thus inherently producing a co-culture of cardiomyocytes, fibroblasts, and endothelial cells. Claim 1 also specifies that the cells are allowed to align and integrate into a tissue or tissue like structure. Neither the claims nor the specification define "align", "integrate", or "tissue-like structure". Therefore, any formation, alignment, or interaction of the cells, such as EB formation, encompasses this limitation. The amendments to the claims further specify that the cardiomyocytes acquire “a longitudinal morphology” upon integration and alignment. “A

longitudinal morphology" is being interpreted to encompass a linear patterned morphology because "longitudinal" encompass lengthwise. Thus, a longitudinal morphology encompasses a lengthwise or linear morphology. More specifically, breadth of a longitudinal morphology encompasses at least two adjacent cardiomyocytes because two points, or in this case two cells, are the minimal requirement for a linear, lengthwise morphology. EB formations comprise at least two adjacent cardiomyocytes, thus an ES will still encompass these limitations.

Muller discloses a method of culturing mouse ES cells to form EBs (p. 2542, col 1, lines1-12), thus disclosing the limitations of claim 1 and 13. These disclosures also disclose the products of claims 15, 16, and 45. These disclosures also disclose the limitations of claim 49 because claim 49 recites an intended use for the method of claim 1 and does not impose further material limitations to the method, therefore does not impose addition patentable limitations. Muller discloses that before EB formation, a EGFP reporter gene operably linked to the cardiac specific promoter, CMVenh/MLC-2v was introduced and expressed by the ES cells (p. 2541, col 2, par 1 under "Transfection constructs", lines 19-22). These disclosures disclose the reporter gene limitations of claims 4, 6, 11, and 26. These disclosures also disclose the selectable marker limitations of claims 2, because a "selectable marker" can be anything that can be used to select, sort, choose, or discriminate a cell and EGFP can be used as such. Further, The claims do not require the "selectable marker" and the "reporter gene" be different entities. Therefore, the EGFP encompasses the limitations of both the selectable marker and reporter gene. As follows, the limitations of claim 5 is also met because the

regulatory sequence of the marker and reporter gene are the same, and thus substantially the same as claimed. The limitations of claims 7 and 8 are met because the marker gene and the reporter gene are on the same nucleic acid molecule and cistron. Further, Muller discloses the use of ES cell transfected with the selectable marker gene, neomycin, operably linked to the cardiac alpha-MHC promoter to select cardiomyocytes and ES cell transfected with the a EGFP reporter gene operably linked the cardiac alpha-MHC promoter to select cardiomyocytes (p. 4541, col 1, lines 20-31). Thus Muller also discloses the use of a separate selectable marker, neomycin, and a reporter gene EGFP. These disclosures also encompass the limitations of claim 70. Claim 70 required that the cell be genetically engineered to express a target gene. The breadth of "a target gene" can be any gene of interest. In the instant case, the neomycin and EGF encompass genes of interest and the cells were genetically engineered to express these genes of interest. Thus, Muller discloses claim 70. Muller discloses method of differentiating ES cell by EB formation and selecting cardiomyocytes from the EB (p. 4542, col 1, par 1. line 1 to par 2, line 8). Although Muller focuses on cardiomyocytes produced by EB formation, Muller acknowledges that this method results in spontaneous differentiation in vitro into a variety of cell lineages including endothelial cells (p. 4540, last line to line 4 of col 1 on p. 4541). Muller does not specifically disclose that the EB differentiate into fibroblasts. However, it is well established in the art that EB produce cell of all cell types and in particular fibroblasts (Itskovitz-Eldor; see p. 94 Figure 5). Thus inherently the EB formation results in a coculture, integration, and alignment of cardiomyocytes, endothelial cell, and fibroblast,

among other cell types in the EB culture. Claim 71 specifies the addition of a compound know to active or inhibit the differentiation process in the culture medium. The breadth of this recitation encompasses the EB cultured medium itself because the culture medium is known to promote or activate EB formation. Muller discloses that the EB or beating areas was subjected to patch-claim experiments in container to analyze their electrophysiological status (p. 4522, col 2, section 'Preparation of single cells and electrophysiology'). These disclosures encompass the limitations of claims 40 and 72. Claim 41 specifies electrical measurement on an array. The breadth of an array encompasses multiple simultaneous measurements on multiple samples. This is taught by the disclosure of electrophysiological analysis. Thus, the limitations of claim 41 are disclosed. Claim 73 specifies taking three or more measurement in claim 1, optionally at three different positions within the container. The claims do not specify what is to be measured and the positions of measurement are optional. Thus any type of measurement will encompass the limitations of this claim. Muller discloses the measurement of alpha-actinin, skeletal myosin, and anti-tropin I expression by immunofluorescence labeling (p. 4542, col 2, par 3 and 4). Muller discloses measurement of cardiomyocytes by FACS analysis (p. 4542, col 2, last par). Muller discloses electrophysiological measurements, as discussed above. Thus, Muller discloses more than three measurements and discloses the limitations of claim 73.

Thus, Muller clearly anticipates the claims because Muller discloses all the patentable limitations of the claims.

Response to Arguments

Applicant's arguments filed 11/12/2009 have been fully considered but they are not persuasive.

Applicant asserts that Muller does not disclose a method of producing cardiac tissue comprising co-culture of cardiomyocytes, endothelial cells, and fibroblasts. Applicant asserts that in particular Muller does not disclose fibroblasts. Applicant's argument is not found persuasive. While Muller does not explicitly disclose that EB cell culture also produces fibroblasts among the endothelial cell and cardiomyocytes. EB spontaneously develop into any and all cell types including fibroblasts (see Itskovitz-Eldor, p. 94, Figure 5). Therefore, Muller's disclosure of EB differentiation culture inherently includes the production of fibroblast in addition to endothelial cells and cardiomyocytes.

Applicant asserts that Muller does not disclose that cardiomyocytes acquire longitudinal morphology upon integration and alignment with fibroblasts and endothelial cells. Applicant's argument is not found persuasive because the claims recite these limitations in a "wherein" clause. Thus, these limitations are not active method steps but rather resulting properties of the culture that occur when completing the active method steps. Ultimately the language of the claims recites that culturing the three cell types together and allowing them to be together results in integration and alignment of the cardiomyocytes with the endothelial cells and fibroblasts as claimed. Muller discloses a method that (a) cultures cardiomyocytes in the presence of endothelial cells and fibroblasts, and (b) allows some sort of alignment and integration of the three cell

types, as the active steps of the method require. Therefore, these method steps should result inherently result in cardiomyocytes acquiring a longitudinal morphology upon integration and alignment with fibroblasts and endothelial cells when the method steps are completed.

Amending the claims to add a step that requires differentiating ES cells to obtain a population of cardiomyocytes before the culturing step may overcome this rejection.

Thus, because Muller still discloses the limitations of the claims and Applicant's argument are not found persuasive, the rejection of record is maintained.

Claims 1, 2, 3-5, 7, 8, 11, 15, 16, 26, 40, 41, 45, 49, and 70-74, as amended or previous presented, are rejected under 35 U.S.C. 102(b) as being anticipated by Franz (US Patent 5,928,943 patent date:7/27/1999).

The instant rejection encompasses the same claim interpretation as discussed in the Muller rejection.

Franz discloses a method of culturing and producing EB with ES cells that comprise an expression vector encoding the selectable marker, neomycin, and the reporter gene, beta galactosidase (beta-Gal) operably linked to the cardiac specific promoter, MLV-2v promoter (col 1, lines 21-23, lines 40-47, lines 52-53, and figure 1). Franz discloses that these ES cells are cultured using the hanging drop method to form EB and that EB cultures are transferred into microtiter plates (col 3, lines 3-23). Franz discloses that expression of beta-Gal identifies cardiomyocytes cells, while expression of the selectable marker allows to a selection of cardiomyocytes differentiating cells

over non-cardiomyocyte differentiating cells at an early stage in differentiation (col 3, lines 21-23 and lines 26-35). Franz discloses that the EB and cells are analyzed for electrophysiological function (col 3, lines 36-40).

Thus Franz clear anticipates the instant claims because Franz discloses all the patentable limitations of the claims.

Response to Arguments

Applicant's arguments filed 11/12/2009 have been fully considered but they are not persuasive. Applicant asserts that Franz is only directed to generation of cardiac muscle cells and does not teach producing cardiac tissue from the coculture and alignment of cardiomyocytes, endothelial cells, and fibroblast. Applicant's argument is not found persuasive because, as discussed above with Muller, the claims encompass an EB culture. While Franz does not discuss the presence and alignment of endothelial cells and fibroblast with cardiomyocytes, these processes occur inherently in EB culture.

Amending the claims to add a step that requires differentiating ES cells to obtain a population of cardiomyocytes before the culturing step may overcome this rejection.

Thus, because Franz still discloses the limitations of the claims and Applicant's argument are not found persuasive, the rejection of record is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3, 6, 42, and 75, as amended or previously presented, are rejected under 35 U.S.C. 103(a) as being unpatentable over Franz (cited above), in further view of Wantanabe (Wantanabe et al. Biochem Biophys Res Com 213(1):130-137, 1995), Muller (cited above) and Feld (Feld et al. Circulation 105:522-529, January 2002).

The instant rejection encompasses the same claim interpretation as discussed in the Muller 102(b) rejection.

Franz teaches a method of culturing and producing EB with ES cells that comprise an expression vector encoding the selectable marker, neomycin, and the reporter gene, beta galactosidase (beta-Gal) operably linked to the cardiac specific promoter, MLV-2v promoter (col 1, lines 21-23, lines 40-47, lines 52-53, and figure 1). Franz teaches that these ES cells are cultured using the hanging drop method to form EB and that EB cultures are transferred into microtiter plates (col 3, lines 3-23). Franz teaches that expression of beta-Gal identifies cardiomyocytes cells, while expression of the selectable marker allows to a selection of cardiomyocytes differentiating cells over non-cardiomyocyte differentiating cells at an early stage in differentiation (col 3, lines 21-23 and lines 26-35). Franz teaches that the EB and cells are analyzed for electrophysiological function (col 3, lines 36-40).

Franz does not teach the selectable marker is a puromycin as claimed in claim 3. However, Watanabe teaches methods for selecting transfected ES cell containing puromycin genes. Thus it would have been obvious to an artisan of ordinary skill to

substitute the neomycin gene of Franz with the functional equivalent, puromycin, taught by Watanabe, in order to achieve the predictable result of selecting transfected functionally drug resistance.

Franz does not teach the EGFP reporter gene as claimed in claim 6. However, Muller teaches the use of ES cell comprising a EGFP gene operably linked to the cardiac specific promoter, MLV-2v promoter, to identify ES cell that differentiate into cardiomyocytes (p. 4541, col 1, lines 20-31). Further Muller demonstrates the superiority of EGFP as a reporter gene because it allows for identification and sorting of live cardiomyocytes by FACS (p. 4542, col 2, last par). Thus, it would have been obvious to an artisan of ordinary skill to simply substitute the beta-Gal reporter gene of Franz with the function equivalent, EGFP gene taught by Muller, in order to achieve the predictable result of expressing cardiomyocyte specific reporter. Further, an artisan would be motivated to do such a substitution because EGFP allows for monitoring and sorting live cardiomyocytes, whereas beta-Gal does not.

Franz does not teach recording the extracellular potential with a MEA, as claimed in claim 42. However, Feld discloses a method of measuring extracellular potential in multicellular cardiac grafts using MEA (p. 523, col 1, section 'Multielectrode Mapping Technique', par 1, line 1 to col 2, lines 2). Thus, it would have been obvious to an artisan of ordinary skill that an artisan to choose MEA, as taught by Feld, from a finite number of predictable methods of measuring extracellular potential with a reasonable expectation of successfully measuring extracellular potential in the tissue cultures of the instant claims.

Franz does not specifically teach the use of 24-, 96-, 384-, or 1586- well plate, as claimed in claim 75. However, at the time of the invention it would have been obvious to an artisan of ordinary skill to choose from a finite number of a micro titer plate designs comprising the number of well needed to accommodate their EB culture of Franz depending upon the intended use of the culture with a reasonable expectation of success.

The combination of prior art cited above in all rejections under 35 U.S.C. 103 satisfies the factual inquiries as set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). Once this has been accomplished the holdings in KSR can be applied (*KSR International Co. v. Teleflex Inc. (KSR)*, 550 U.S. ___, 82 USPQ2d 1385 (2007): "Exemplary rationales that may support a conclusion of obviousness include: (A) Combining prior art elements according to known methods to yield predictable results; (B) Simple substitution of one known element for another to obtain predictable results; (C) Use of known technique to improve similar devices (methods, or products) in the same way; (D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results; (E) "Obvious to try" - choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success; (F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art; (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary

skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention."

In the present situation, rationales A-E and G are applicable. The claimed method was known in the art at the time of filing as indicated by Franz, Wantanabe, Muller, and Feld. Thus, the teachings of the cited prior art in the obviousness rejection above provide the requisite teachings and motivations with a clear, reasonable expectation. The cited prior art meets the criteria set forth in both Graham and KSR.

Response to Arguments

Applicant's arguments filed 11/12/2009 have been fully considered but they are not persuasive.

Applicant asserts that the art presented in the 103 rejection would not have provided a reasonable expectation of success in obtaining the method of the invention. Applicant refers to Examples 2-5 to demonstrate that the method of the invention relies upon the culture of the endothelial cells and the fibroblast with the cardiomyocytes to produce functional cardiac tissue. Applicant assert that the art of Franz and Muller only teach the generation of cardiomyocytes from ES cells which would not produce functional cardiac tissue.

Applicant's arguments are not found persuasive because while it may be the intent of Applicant to capture the invention of the working Examples, the invention of the claims more broadly encompasses other embodiments than those disclosed in the Examples. As discussed above, the breadth of the claims encompass an EB culture.

The claims require culturing cardiomyocytes in the presence of fibroblasts and endothelial cells and allowing the integration and alignment of the three cell types. An EB culture as discussed above is encompassed by the breadth of these claims. However, the working examples more narrowly disclose a method that produces cardiomyocytes from EBs, isolates that cardiomyocytes from the EBs and further cultures the isolated cardiomyocytes with fibroblasts in a new culture. It is noted the working examples cited by the Applicant do not even introduce endothelial cells into the culture. Therefore, while the invention of the examples is encompassed by the claims, the breadth of the claims does not limit the claims to the disclosure of the examples. Therefore, Applicant is not reading the claims to its fullest breadth and Muller and Franz would have a reasonable expectation of accomplishing the active method steps of the claims. If Applicant is stating that the Muller and Franz will not result in the proper outcome of the method, Applicant has not provide the appropriate active method step to produce the intended product. The claimed method step is required to provide the appropriate active step that will lead the intended product.

Applicant asserts that neither Wantanabe nor Feld suggest co-culturing cardiomyocytes, endothelial cells, and fibroblasts. Applicant's arguments are not found persuasive because Wantanabe and Feld were not provided to teach the specifics of the culture because that is taught by Muller and Franz. Feld was provided to demonstrate that MEA technology exist in the prior art and that there is a reasonable expectation of success in applying it to the cardiac cell outgrowths from the EBs of Franz or Muller. Wantanbe was provided to demonstrate that the various claimed

microtiter plates exist in the art and are readily available for use in the EB cultures of Muller or Franz with a reasonable expectation of success.

Therefore, because Applicant's arguments are not persuasive in overcoming the rejection of record and the breadth of the claims still encompass the teaching of the art, the obviousness 103a rejection of record is maintained.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-8, 11, 15, 16, 26, 40-42, 45, 49, and 70-75, as amended or previously presented, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 and its depend claims recite, "a tissue-like structure". This recitation is indefinite because it is not apparent how closely and in what manner the structure is to resemble a tissue. Amending the claims to include specific structural properties that make a "tissue-like structure" may be remedial.

Response to Arguments

Applicant's arguments filed 11/12/2009 have been fully considered but they are not persuasive. Applicant asserts that an ordinary artisan would understand what is

meant by "a tissue-like structure". Applicant's arguments are not found persuasive because the specification does not define the structural elements that define a tissue-like structure and it is not apparent from the specification or claims how a "tissue-like structure" structurally differs from a tissue. Therefore, a tissue-like structure is indefinite because the structural elements that define a tissue like structure are not apparent.

The following rejections and objections are necessitated by the amendments to the claims:

Claim Objections

Claims 1, 15 and 72 are objected to because of the following informalities:

Amended claim 1 and its dependents recites, "differentiated cardiomyocytes", "differentiated endothelial cells", and "differentiated fibroblasts". Cardiomyocytes, endothelial cells, and fibroblast are examples of terminally differentiated cells. Thus, it is redundant to recite that they are "differentiated". Amending the claims to remove recitations of "differentiated" from claim 1 would be remedial.

Amended claim 15 recites, "cellsobtainable", in line 2. This is being interpreted as a typographic error. Applicant should amend the claim to recite, "cells obtainable".

Amended claim 72 recites, "wherein said one or more cells or cardiac tissue are contained in a container". Claim 72 now depends upon claim 1 which recites cardiomyocytes, endothelial cells, and fibroblast. Thus, clearly the claim 72 requires more than "one cell". To make claim 72 consistent with claim 1, Applicant should

amend the claims to recite "the cells or cardiac tissue" or "the cultured cells or cardiac tissue".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter

Claims 1-8, 11, 15, 16, 26, 40-42, 45, 49, and 70-75 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Amended claim 1 and its dependents now recites, "wherein said cardiac tissue....exhibit...cross-striation". Therefore, amended claim 1 is drawn to an in vitro culture method that produces cardiac tissue that exhibit "cross-striation". The specification as originally filed does not provide explicit or implicit support for such an in vitro method. The specification discloses an in vitro method of producing cardiac tissue that has contractility (p. 44, Example 2, lines 33-34). The specification also teaches an

in vivo method that co-administers cardiomyocytes and fibroblast into a cryoinfarcted heart. The specification further teaches that after said co-administration the implanted cardiomyocytes implanted in the heart displayed cross striation (p. 45, Example 3, lines 14-22). In contrast, the specification fails to disclose an in vitro culture of cardiomyocytes, endothelial cells, and fibroblast that result in a cardiac tissue exhibiting cross-striation, as claimed. Thus, the specification does not support such recitations and the instant recitation constitutes new matter.

Response to Arguments

Applicant's arguments filed 11/12/2009 have been fully considered but they are not persuasive. Applicant asserts that support for the amendment to claim 1 is found in Examples 2, 3, and 5 and figures 4 and 6.

As discussed above, Example 2 discloses an in vitro method of culturing cardiomyocytes and fibroblasts. Example 2 does not disclose the resultant cardiac tissue exhibits cross striation. Therefore, Example 2 does not provide support for amended claim 1.

As discussed above, Example 3 discloses an in vivo method, whereas the claims are drawn to an in vitro method. Thus, Example 3 does not provide support for amended claim 1. Example 5 discloses genetic modification of ES cell that are then differentiated in EB. Cardiomyocytes are isolated from the EBs and co-cultured with fibroblasts. Example 5 does not teach that the cardiac tissue exhibits cross striation. Therefore, Example 5 does not provide support for amended claim 1.

Figures 4 and 5 disclose the co-cultures but do not demonstrate cross striation. Therefore, figures 4 and 5 do not support the amendment to claim 1.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Scope of Enablement

Claims 1-8, 11, 15, 16, 26, 40-42, 45, 49, and 70-75 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of modeling or obtaining cardiac tissue or cardiac tissue-like structures comprising (a) culturing cardiomyocytes in the presence of fibroblasts and endothelial cells and (b) allowing integration and alignment of said cardiomyocytes, fibroblasts, and endothelial cells into cardiac tissue, wherein said cardiomyocytes acquire longitudinal morphology upon integration and alignment with fibroblasts and endothelial cells, and wherein said cardiac tissue exhibit contractility and cross striation, does not reasonably provide enablement for a method that uses differentiating cardiomyocytes, differentiating fibroblasts, differentiating endothelial cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make or use the claimed invention, if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue".

Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The claims recite, "differentiating cardiomyocytes", "differentiating fibroblasts", and "differentiating endothelial cells". However, these recitations are in consistent with the teachings of the art. "Cardiomyocytes", "fibroblasts", and "endothelial cells" are all examples of terminally differentiated cells. By definition, a "differentiated cell" can not be "differentiating" because they have completed the process of differentiation. Cardiomyocytes, fibroblasts, and endothelial cells have completed the process of differentiation. Therefore, these cells by definition can not be differentiating as claimed.

The specification discloses the use of ES cells and differentiating them to obtain cardiomyocytes. The specification also discloses obtaining embryonic fibroblast. However the specification fails to provide specific guidance to teach a means of differentiating cardiomyocytes, fibroblast or endothelial cells.

Thus, the specification and art fail to enable "differentiating cardiomyocytes", "differentiating endothelial cells" and "differentiating fibroblasts" because the art teaches that this cell types are terminally differentiated and thus do not undergo differentiation and the specification fails to provide specific guidance to teach "differentiating" cardiomyocytes, endothelial cells, and fibroblasts. Therefore, the specification only enables the use of cardiomyocytes, endothelial cell, and fibroblasts in a co-culture method to produce cardiac tissue.

Therefore at the time of filing the skilled artisan would need to perform an undue amount of experimentation without a predictable degree of success to implement the invention as claimed.

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARCIA S. NOBLE whose telephone number is (571)272-5545. The examiner can normally be reached on M-F 9 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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